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PRIMER

Mixed Cardiogenic Shock: A Proposal for Standardized Classification, a Hemodynamic Definition, and Framework for Management

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ABSTRACT: The classification of cardiogenic shock (CS) has evolved from a singular cold-and wet-hemodynamic profile. Data from registries and clinical trials have contributed to a broader recognition that although all patients with CS have insufficient cardiac output leading to end organ hypoperfusion, there is considerable variability in CS acuity, underlying etiologies, volume status, and systemic vascular resistance. Mixed CS can be broadly categorized as *CS with at least 1 additional shock state*. Mixed CS states are now the second leading cause of shock in contemporary coronary intensive care units, but there is little high-quality evidence to guide routine care, and there are no standardized classification frameworks or well-established hemodynamic definitions. This primer summarizes the current epidemiology and proposes a classification framework and invasive hemodynamic parameters to guide categorization that could be applied to help better phenotype patients captured in registries and trials, as well as guide management of mixed CS states.

Key Words: cardiogenic shock ■ hypovolemic shock ■ mixed shock ■ vasodilatory shock

EPIDEMIOLOGY OF MIXED CARDIOGENIC SHOCK

Mixed cardiogenic shock (CS), which can be classified as *CS with at least 1 additional contributing cause of shock state*, is common. Low systemic vascular resistance (SVR) is common in patients admitted with CS and is associated with a systemic inflammatory response–like syndrome.[1,2] It is important to note that low SVR has been reported to be associated with higher short-term mortality. Patients are commonly culture-negative because of sterile vasoplegia, which is often attributed to myonecrosis and/or cytokine release.[2,3] Culture-positive sepsis occurs less frequently in mixed CS with low SVR, but portends a worse prognosis compared with sterile vasoplegia. Among patients living with heart failure, infections are the second leading cause of hospital admission (25%) and a leading cause of death (14%–24%).[4–6] An analysis of the of the Nationwide Readmission Database reported that 19% of patients with septic shock have concurrent heart failure, which is independently associated with a higher risk of acute kidney injury, stroke, and in-hospital death.[7] In patients admitted with an acute ST-segment–elevation myocardial infarction (MI), concurrent infection is uncommon (2.4%), but is associated with a nearly sixfold risk mortality.[8] In MI-associated CS, the reported incidence of sepsis has risen to 11.5% and is associated with higher in-hospital mortality and health care costs, as well as longer hospital length-of stays.[9]

The 2017 American Heart Association Scientific Statement on CS and the 2023 Shock Academic Research Consortium (SHARC) have designated mixed CS as a distinct shock phenotype.[10,11] Mixed CS is now the second most common form of shock in contemporary cardiac intensive care units (CICUs).[12,13] The Critical Care Cardiology Trials Network (CCCTN) reported that 20% of all patients with shock admitted to contemporary

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.124.069508.
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Nonstandard Abbreviations and Acronyms

APACHE	Acute Physiology and Chronic Health Evaluation
CCCTN	Critical Care Cardiology Trials Network
CICU	cardiac intensive care unit
CO	cardiac output
CS	cardiogenic shock
CULPRIT-SHOCK	Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock
LV	left ventricular
MI	myocardial infarction
PAC	pulmonary artery catheter
PACCS	Pulmonary Artery Catheter in Cardiogenic Shock
PCI	percutaneous coronary intervention
RV	right ventricular
SCAI	Society for Cardiovascular Angiography & Interventions
SHARC	Shock Academic Research Consortium
SHOCK	Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
SOAP II	Sepsis Occurrence in Acutely Ill Patients II
SOFA	Sequential Organ Failure Assessment
SVR	systemic vascular resistance
tMCS	temporary mechanical circulatory support
TTE	timely transthoracic echocardiography
VA-ECMO	veno-arterial extracorporeal membrane oxygenation

CICUs have mixed CS.[12] It is important to note that these patients had a higher burden of comorbidities, clinical acuity, provision of critical care restricted therapies, and all-cause in-hospital mortality rate. These data potentially highlight the importance of timely recognition of mixed CS and its underlying etiologies; however, little guidance is available to help direct appropriate classification and management of this high-risk and complex patient population.

PROPOSED DEFINITION

In patients with a classic CS phenotype, to maintain arterial blood pressure, the SVR typically increases to compensate for a low cardiac output (CO). However, registry studies have reported that SVR response is variable.[2,14–16] A drop in SVR is pathognomonic for vasodilatory shock states irrespective of the cause, but the expected compensatory CO response can vary.[17,18] A recent cohort study of 1488 patients with isolated CS reported that the median SVR was 1256 (interquartile range, 899–1688) dynes*sec*cm^{-5}.[3] Hemodynamic parameters of (lower) systemic arterial tone (eg, SVR) and (impaired) right ventricular (RV) function were independently associated with higher all-cause in-hospital mortality, whereas CO and cardiac power output were not.

We propose broadly defining mixed CS as *CS with at least 1 additional shock state.* Cardiac-vasodilatory shock is the most common form of mixed CS and can be defined as *an inappropriate compensatory hemodynamic response to the primary cause of shock* (Figure 1). Although we do not use strict thresholds to hemodynamically define mixed CS, given that "inappropriate" should be interpreted in the context of the concurrent vasoactive medications that modulate SVR and CO, we propose that the following hemodynamic parameters should prompt the consideration and evaluation of a mixed CS state. In primary CS, a low or normal SVR (eg, <1000–1200 dynes*sec/cm^5) or SVR index (eg, <2000–2400 dynes*sec/cm^5/m^2) may be considered suggestive of a mixed CS state with a contribution of systemic vasodilation. In patient with primary vasodilatory shock, a normal or inappropriately or cardiac index (eg, <2.5 L/min/m^2) or low CO (eg, <6 L/min) with adequate volume resuscitation, and particularly in the presence of elevated diastolic intracardiac pressures (central venous pressure ≥8–12 mm Hg and/or pulmonary capillary wedge pressure ≥12–15 mm Hg), should prompt consideration of a secondary cardiac contribution to the cause of shock. It is also usually necessary to take concurrent vasoactive medications into account when estimating what the SVR/SVR index and CO/cardiac index would be if the vasoactive medications were not present.

PROPOSED CLASSIFICATION FRAMEWORK OF MIXED SHOCK STATES

We propose dichotomizing the classification of *mixed CS* based on the primary or dominant of cause of shock as either primary cardiogenic with a secondary shock pathogenesis *or* primary non-CS with secondary CS (Figure 2). In this framework, primary CS may still be phenotyped according to the 4 SHARC groups of acute MI, heart failure, postcardiotomy, and secondary (ie, arrhythmia, valvular, or pericardial) CS, followed by the secondary shock contributor (eg, sterile vasoplegia, sepsis, hemorrhagic/hypovolemic).[11] Common secondary forms of shock in the CICU include vasodilation

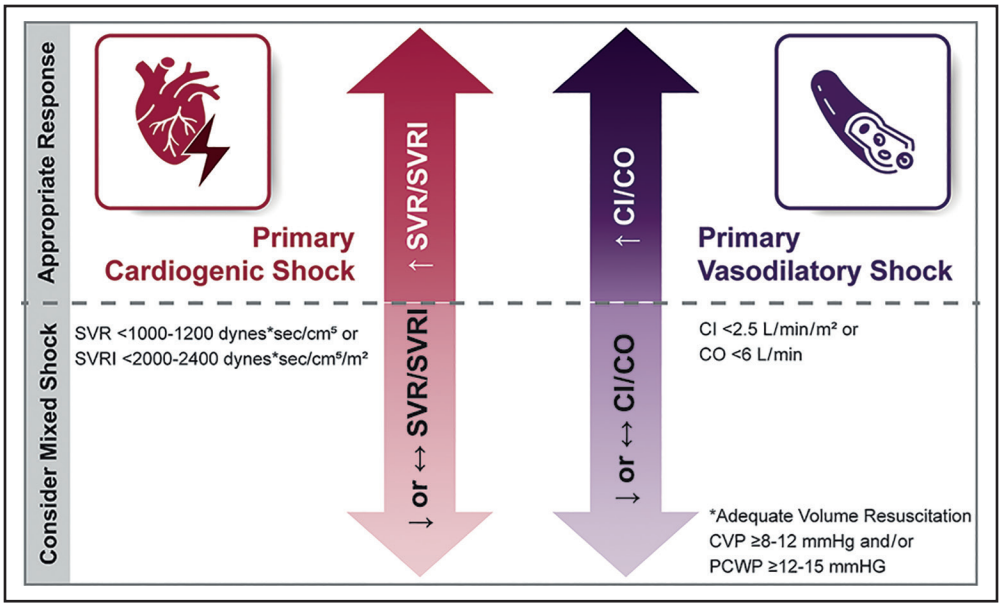

Figure 1. Normal hemodynamic compensation and proposed criteria for mixed cardiac-vasodilatory shock.
*Adequate volume resuscitation. Central venous pressure (CVP) ≥8 to 12 mm Hg or pulmonary capillary wedge pressure (PCWP) ≥12 to 15 mm Hg. Mixed cardiac-vasodilatory shock constitutes the majority of mixed cardiogenic shock cases and presumes adequate volume status. CI indicates cardiac index; CO, cardiac output; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; and SVRI, systemic vascular resistance index.

(eg, sterile vasoplegia, sepsis, intravenous vasoactive agents or preadmission heart failure pharmacotherapy, and postcardiopulmonary bypass), hypovolemic or hemorrhagic, and endocrine shock (eg, critical illness–related corticosteroid insufficiency). Similarly, in primary non-CS, the noncardiac cause (eg, sepsis, toxidromes, endocrine shock, or hypoxemia or hypotension associated coronary hypoperfusion) would precede the description of the secondary cardiogenic cause (eg, septic cardiomyopathy, pre-existing heart failure, secondary myocardial

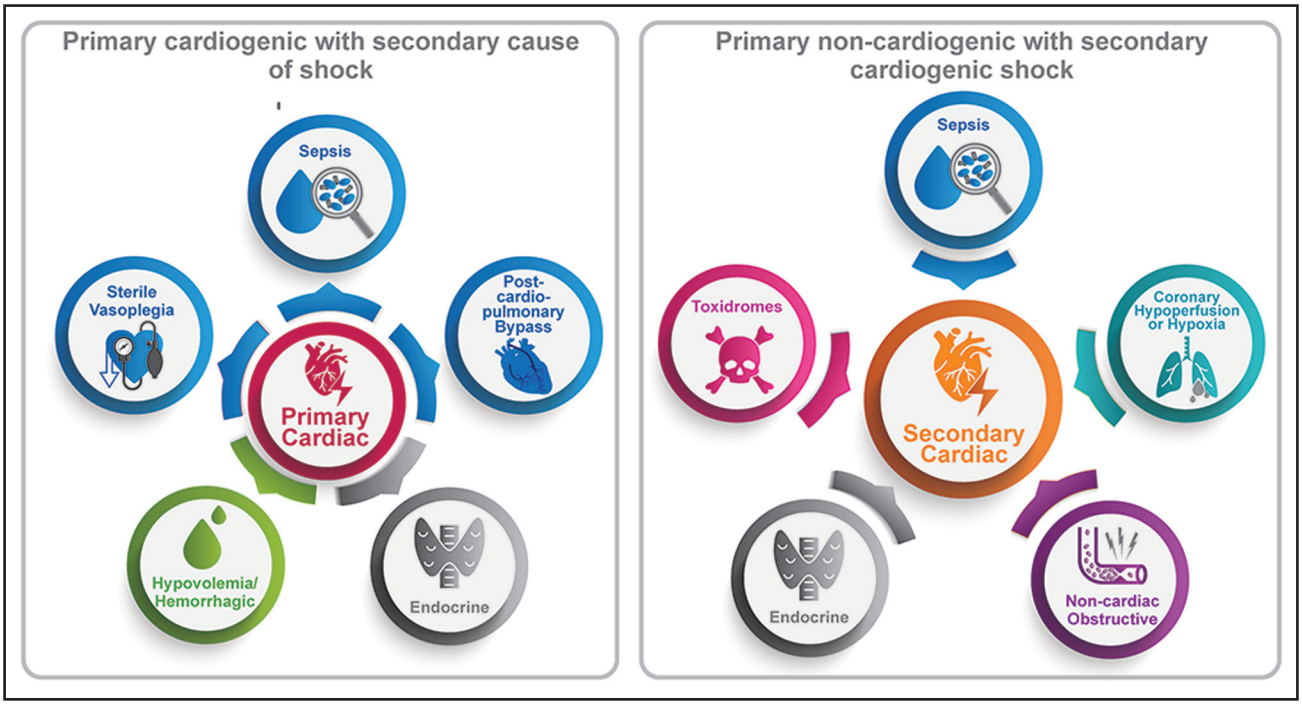

Figure 2. Common causes of mixed cardiogenic shock states in cardiac intensive care units.
Left, Primary cardiogenic shock with surrounding common secondary causes of noncardiogenic shock. **Right**, Primary noncardiogenic causes of shock in the periphery that may lead to secondary cardiogenic shock.

dysfunction, or valvular disease) that results in an inadequate compensatory cardio-hemodynamic response. In this framework, obstructive shock caused by a cardiogenic cause (eg, tamponade, constriction, pulmonary embolism) would still be classified under CS. Noncardiogenic obstructive shock (eg, tension pneumothorax or abdominal compartment syndrome) contributors to mixed shock states are uncommon in the CICU population, but should be considered in a diagnostic approach to mixed shock states (Figures 2 and 3). Future research could help define the relative incidence and outcomes associated with these individual mixed CS states.

PATHOPHYSIOLOGY OF VASODILATORY SHOCK AND SEPTIC CARDIOMYOPATHY

The prevalence of the systemic inflammatory response in patients with CS ranges from 17% to 50%.[1,19] Although distributive shock in patients with primary CS was historically thought to be mediated by sepsis, up to 74% of patients are culture-negative.[2] In addition, myonecrosis caused by an acute MI, resuscitation from cardiac arrest, and blood transfusion can trigger a systemic inflammatory response through a cytokine cascade that lowers SVR, leading to the downward spiral of mixed shock with systemic hypoperfusion.[20,21] Vasoplegia is also a recognized hemodynamic evolution after initiation of temporary mechanical circulatory support (tMCS) but remains poorly understood.[22,23] In addition, patients with CS may develop a secondary distributive shock without systemic inflammatory response from critical illness–related corticosteroid insufficiency and vasodilatory medication use (eg, sedatives).

Sepsis (broadly defined as a life-threatening dysregulated host response to infection) is the most common cause of distributive shock; however, up to 70% of patients with septic shock have myocardial dysfunction, which may result in mixed CS.[24,25] Although a universally accepted definition of septic cardiomyopathy is lacking, it can be practically defined as an acute de novo sepsis associated syndrome of cardiac dysfunction not caused

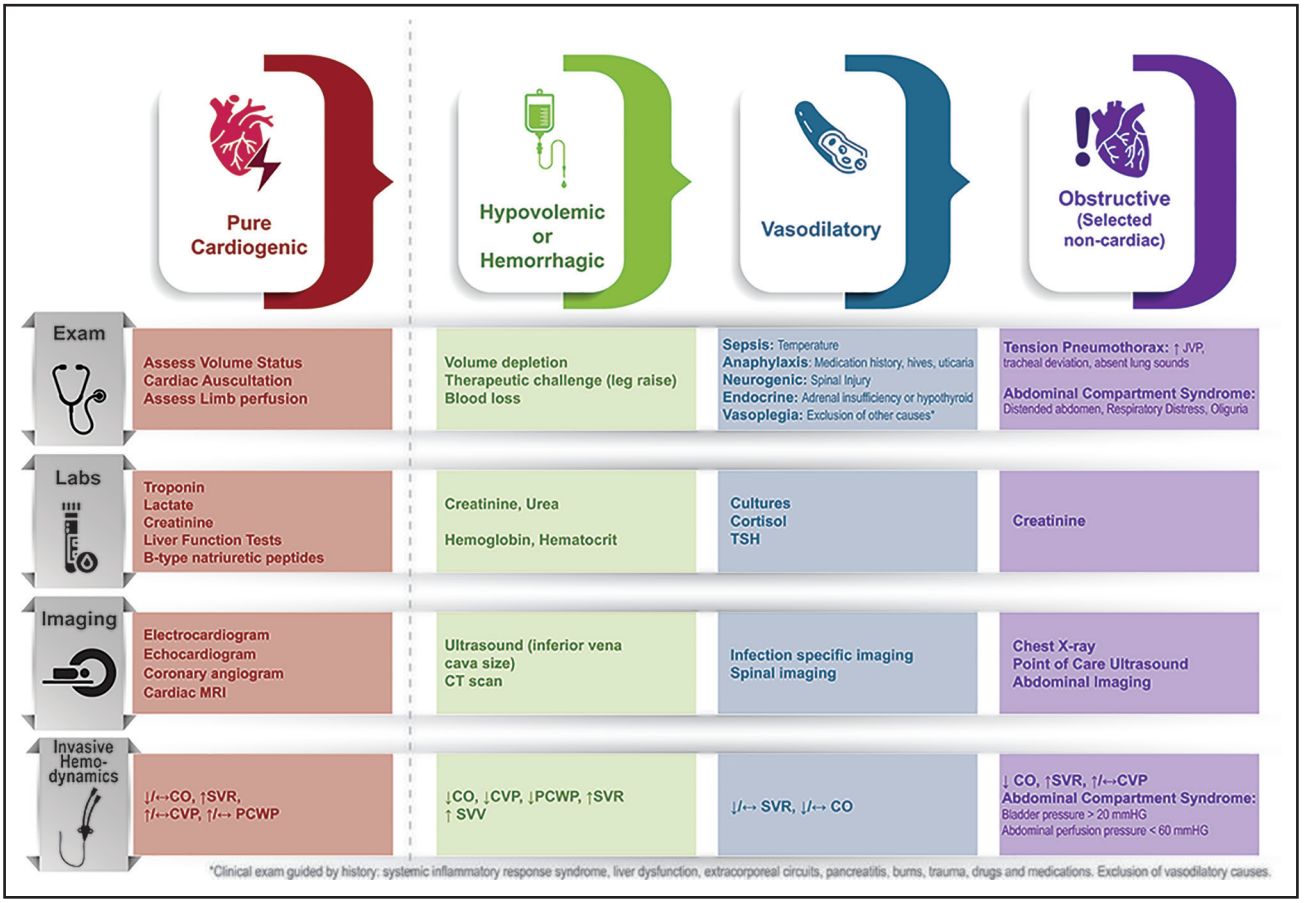

Figure 3. Key elements of a comprehensive approach to evaluation of suspected mixed cardiogenic shock in the cardiac intensive care unit.

*Clinical examination guided by history: systemic inflammatory response syndrome, liver dysfunction, extracorporeal circuits, pancreatitis, burns, trauma, drugs, intravenous vasoactive agents, and preadmission medications. CO indicates cardiac output; CT, computed tomography; CVP, central venous pressure; JVP, jugular venous pressure; MRI, magnetic resonance imaging; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; SVV, stroke volume variation; and TSH, thyroid stimulating hormone.

by undiagnosed/untreated coronary ischemia or acute valvular disease.[25] It may present as systolic, diastolic, or hyperdynamic dysfunction (including left ventricular [LV] outflow tract obstruction) of either the left or right ventricle. The postulated pathophysiologies include acute cardiac effects of the infectious organism (pathogen associated molecular patterns), secondary inflammation (damage associated molecular patterns and cytokine release), the vascular effects of septic shock (nitric oxide release and mitochondrial dysfunction), and cardiac specific effects of septic shock (abnormal cardiac calcium handling). In practice, distinguishing septic from a stress-induced cardiomyopathy may be difficult, but the latter may have a unique sympathetic or catecholaminergic pathogenesis. The short- and long-term prognoses of patients with septic cardiomyopathy are unclear, but small cohort studies suggest that the mortality in this group can approach 70% with the potential for myocardial recovery among survivors.[26] Currently, there are no specific treatments for this entity, other than treatment of the underlying sepsis and supportive care together with vasoactive agent selection in shock management.

RISK STRATIFICATION

The Society for Cardiovascular Angiography & Interventions (SCAI) classification of CS has been endorsed by multiple international cardiovascular and critical care societies as a universal dynamic CS staging system.[27] It has subsequently been prospectively and retrospectively validated >10 times in multiple critical care environments and phases of care, but it has less robust discrimination outside the CICU.[27–30] Similarly, the Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) score are well validated risk scores with excellent discrimination in medical and surgical intensive care patients, but have modest discrimination or calibration in patients with primary cardiovascular illness.[31–33] A CCCTN analysis evaluating clinician versus algorithmic application of SCAI classes reported that mixed shock made up 28% of all CICU shock admission and that higher SCAI shock classes, from B through E, were associated with an increasing gradient of mortality risk among patients with mixed shock.[34] In addition, in a single-center retrospective cohort study of mixed septic-CS, admission SCAI shock stage had better discrimination for in-hospital mortality compared with SOFA (0.68 versus 0.64; *P*=0.04) and comparable discrimination to APACHE III (0.68 versus 0.72; *P*=0.1). Both the SCAI and APACHE III score could be used to risk-stratify patients with mixed CS, but the modest discrimination of these scores highlights the potential need for novel dedicated risk scores that incorporate traditional CS *and* distributive/sepsis shock risk factors together with measures of frailty and invasive hemodynamic profiles to improve risk prediction in this high-risk cohort.

MONITORING AND MANAGEMENT SUGGESTIONS

Proposed Workup for Common Secondary Causes of Mixed Shock

In patients presenting with primary CS or vasodilatory shock, a simplified hemodynamic approach to identify a secondary contributing form of shock based on invasive hemodynamic parameters is provided in Figure 4. A detailed diagnostic approach incorporating physical examination, laboratory values, echocardiography and imaging, and hemodynamic parameters in provided in Figure S1.

Hemodynamic Monitoring

Placement of an arterial line and a central venous line is suggested in all patients presenting with CS and mixed CS.[10] Timely transthoracic echocardiography is a valuable tool that can be used to help quantify CO, support a diagnosis of myocardial ischemia, and identify LV, RV dysfunction, structural heart disease, or mechanical complications.[10] Noninvasive CO monitors that use pulse contour analysis to estimate CO and SVR are low-risk, are easy to set up, and in mixed shock states may help identify the dominant form of shock and guide therapeutic decision-making, but they have some important limitations including common sources of error in cardiovascular diseases (eg, arrhythmia, aortic regurgitation, and peripheral artery disease); lack information about RV performance, pulmonary pressures, pulmonary resistance, and wedge pressures; and poor correlation with thermodilution in patients with CS.[35] The pulmonary artery catheter (PAC) is potentially valuable in patients with undifferentiated or mixed CS phenotypes; in addition to providing prognostically important information, they can help diagnose primary cardiogenic, vasodilatory, and mixed shock. In patients with CS, the PAC can further differentiate between LV-dominant, RV-dominant, and biventricular shock. Further, in our experience, a PAC may be useful in guiding the balance of vasoconstricting and inotropic pharmacotherapies to optimize perfusion in patients with mixed CS. Use of a PAC should be considered in patients with a suspected cardiogenic contribution and severe or refractory shock not responding to initial therapy.[10,36] Recent observational data have reported an association between PAC use and reduced mortality in patients with CS, especially if a complete assessment of hemodynamic data was performed.[36,37] The ongoing randomized PACCS (Pulmonary Artery Catheter in Cardiogenic Shock) trial (NCT05485376) is seeking to further evaluate the efficacy and safety of PAC in the population with CS.

Role of Percutaneous Coronary Intervention

In patients with CS caused by acute MI, immediate revascularization of the culprit lesion is recommended based on the SHOCK (Should We Emergently

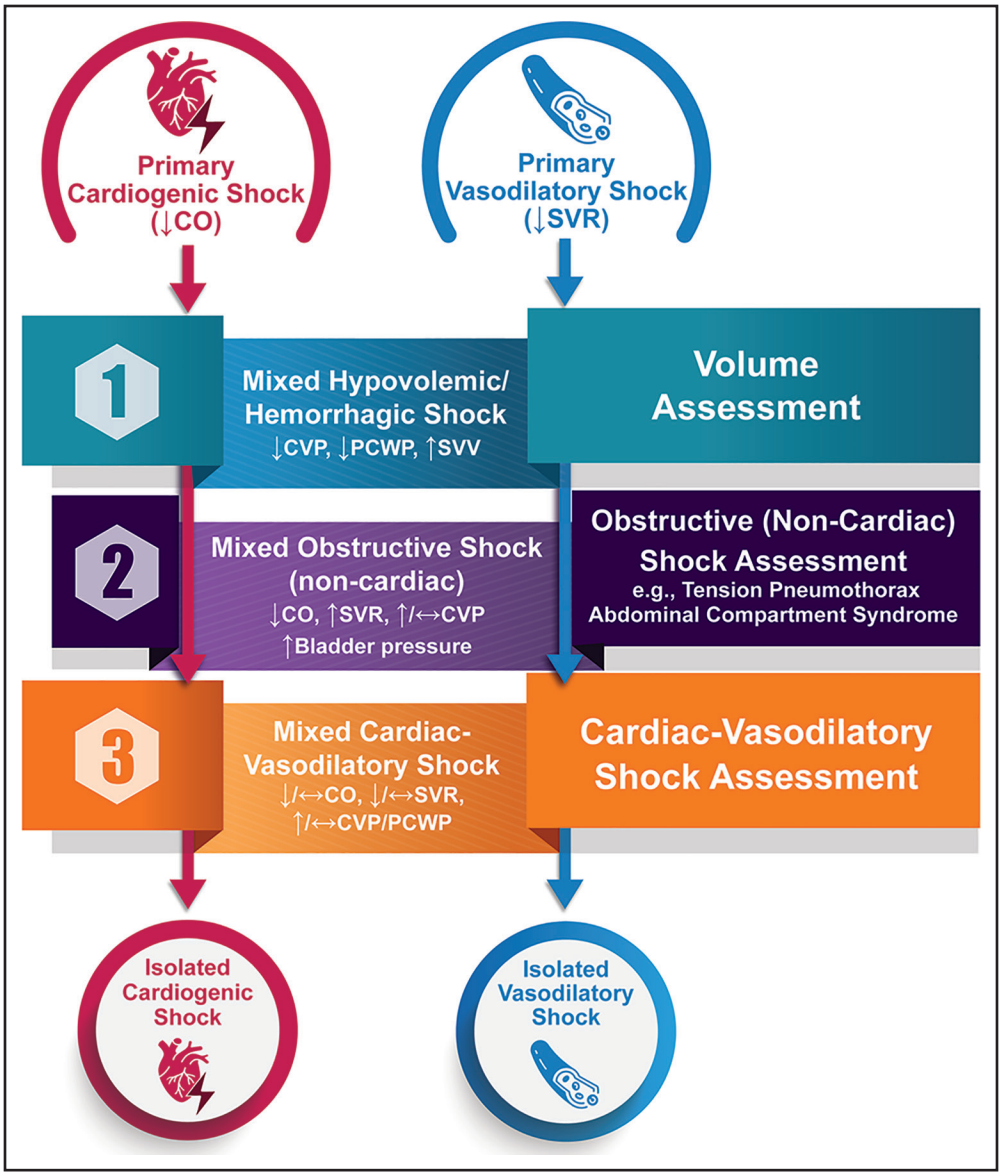

Figure 4. Simplified approach to identifying mixed shock states in patients presenting with primary cardiogenic or vasodilatory shock in the cardiac intensive care unit using invasive hemodynamic parameters.
CO indicates cardiac output; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; and SVV, stroke volume variation.

Revascularize Occluded Coronaries for Cardiogenic Shock) trial, which reported lower 6-month mortality in patients in the early invasive arm (who primarily underwent revascularization with percutaneous coronary intervention [PCI] compared with initial medical stabilization).[38] In patients with MI associated CS with multivessel disease, PCI during the index procedure should be restricted to the infarct-related artery, with consideration for staged PCI of other non–infarct-related arteries. These recommendations are based on the results of the randomized CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial, which reported a lower risk of 30-day death or renal failure requiring renal replacement therapy in infarct-related artery–only PCI arm.[39] In patients with mixed CS with either an ST-segment–elevation MI or a non–ST-segment–elevation MI, thought to be a result of a type 1, 4a, 4b, or 5 MI, we suggest an early invasive approach and revascularization of the infarct-related artery in patients with multivessel disease. In patients with mixed CS with a presumed type 2 MI, there is a paucity of data to guide optimal care, and initial medical management is reasonable.

Pharmacological Management

There is a lack of high-quality evidence to guide interventions for patients with mixed shock. A proposed

 Circulation. 2024;150:1459–1468. DOI: 10.1161/CIRCULATIONAHA.124.069508

approach to fluid, inotropic, and/or vasopressor therapies for patients with mixed CS states using invasive hemodynamic parameters is provided in Figure 5. In patients with a hypovolemic contribution to inadequate CO, cautious fluid resuscitation is appropriate. The use of vasoactive medications is driven by their anticipated physiological effects on contractility and SVR in response to the clinician's interpretation of the underlying predominant hemodynamic abnormalities and invasive hemodynamic parameters, when available. For patients with a mixed cardiogenic and distributive shock, emphasis on agents that both support contractility and mitigate distributive shock is reasonable. In this context, norepinephrine is the preferred vasoactive agent in most patients with a "warm-and-wet" phenotype and is reasonably supported by data from the SOAP II (Sepsis Occurrence in Acutely Ill Patients II) trial in all-comers with shock.[40] Epinephrine is an alternative, but given that a small trial and observational data have raised concerns about possible adverse outcomes with epinephrine, there is a need for comparative prospective trials to address this gap in evidence.[41] Use of inodilating agents, such as dobutamine and milrinone, may sometimes be used in conjunction with norepinephrine or vasopressin,[42] but are rarely appropriate as singular vasoactive therapy in patients with mixed cardiogenic and distributive shock because of their vasodilating effects. We suggest early and serial clinical, laboratory (including lactate clearance), invasive hemodynamic, or echocardiographic reassessment after pharmacotherapeutic changes and particularly initiating an inodilator because of the potential heterogeneity in the hemodynamic response. Scavengers for nitric oxide (methylene blue and hydroxocobalamin) are generally reserved for cases of profound overlying distributive shock, eg, in patients in postcardiotomy shock with vasoplegia or calcium channel blocker overdose.[43]

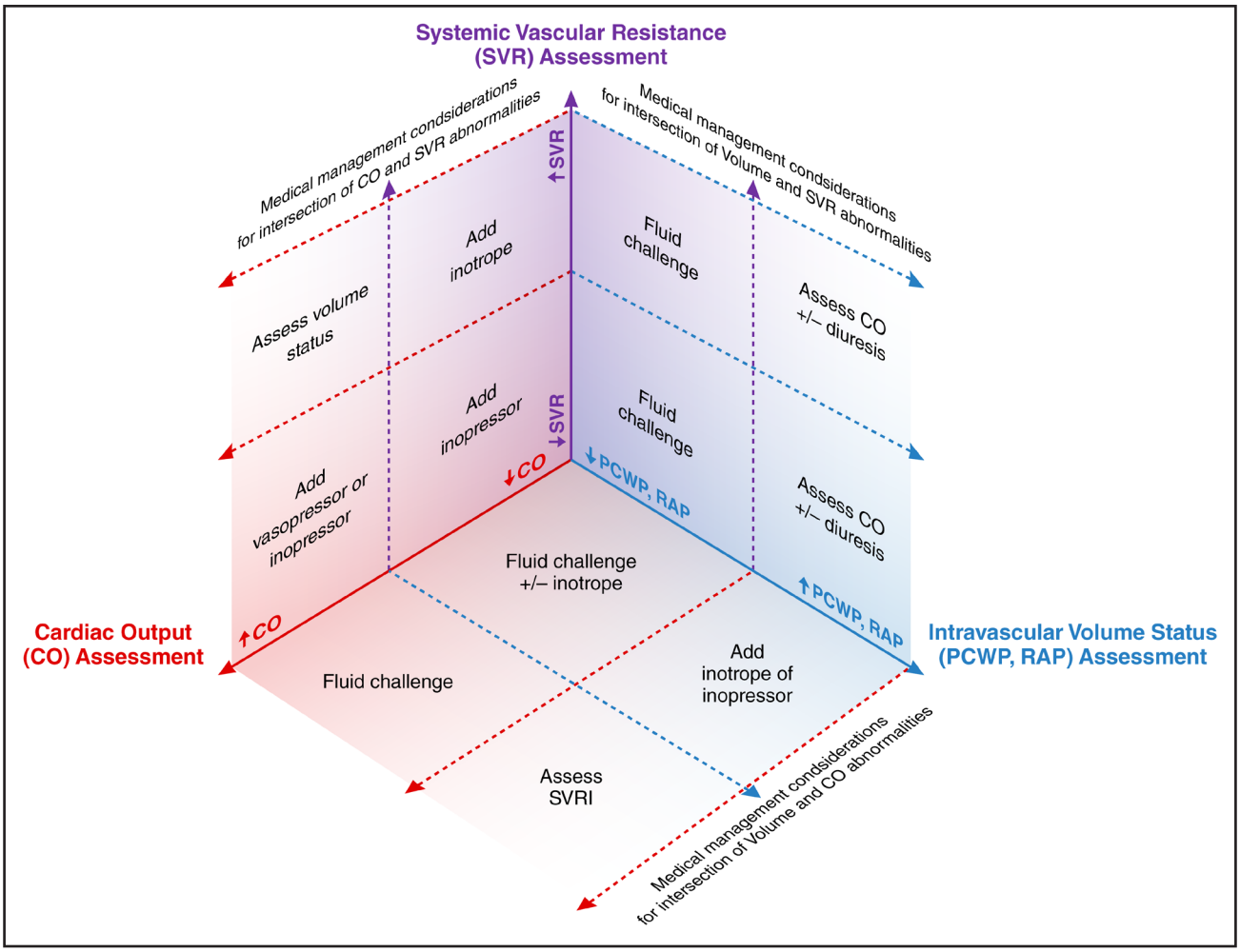

Figure 5. Medical management considerations in response to invasive hemodynamic assessment of volume status, cardiac output, and systemic vascular resistance in patients with mixed cardiogenic shock.
Interpretation guide: the graph presents 3 key invasive hemodynamic variables (CO, SVR, and volume status) on each axis. The 3 quadrants outline potential management strategies when considering the intersection between 2 of the 3 hemodynamic variables. CO indicates cardiac output; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; and SVR, systemic vascular resistance.

Temporary Mechanical Circulatory Support

In patients with CS, the goal of tMCS devices is to support systemic perfusion while minimizing the use of vasopressors and inotropes. There is a lack of randomized data to support tMCS in the mixed CS population, but current epidemiological data from the CCCTN have reported that tMCS devices are used in 22% of patients with mixed CS.[12] When the mixed CS is predominated by vasodilation, there is not a strong rationale for implementation of tMCS given that it may not address (and may even exacerbate) the primary problem. However, the use of tMCS may sometimes be considered by clinicians when there is inadequate cardiac reserve to maintain systemic perfusion in the face of a reversible cause of distributive shock, eg, sepsis with underlying severe cardiomyopathy. The potential advantages and disadvantages of tMCS in mixed shock states are highlighted in Figure S1.

There are no comparative data to direct selection among options for tMCS. Given the unique hemodynamic profile of individual devices, there is a potential hierarchy of which devices are best suited for mixed CS. Notwithstanding, the use of an intra-aortic balloon pump, which augments CO through afterload reduction, may not be appropriate for this phenotype of shock. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has a greater capacity to augment systemic blood flow compared with other tMCS devices; thus, it may be theoretically more advantageous than other tMCS in patients with severe vasoplegia who require a high CO to maintain systemic arterial blood pressure. Although the increased afterload with VA-ECMO is often deleterious in pure CS, this hemodynamic change may be better tolerated in patients with mixed CS. In addition, VA-ECMO can lead to short-term improvements in LV function because of correction of acid-base derangements and increased myocardial oxygen delivery. LV venting in patients on VA-ECMO has the potential to reduce LV end-diastolic pressure, improve oxygenation, reduce LV afterload, and further improve coronary perfusion. It is important to note that the potential physiologic benefits of VA-ECMO must be counterbalanced by the potential risks, which include triggering an inflammatory response that can precipitate vasodilation. Blood exposure to an ECMO circuit can result in a coagulation and inflammatory cascade that can lead to endothelial injury, disrupted microcirculation, and end-organ dysfunction.[44] These risks may be uniquely amplified in patients with a low SVR from sterile vasoplegia and in patients with mixed cardiogenic and septic shock with a dysregulated host response to an infection.

Although the American College of Critical Care Medicine recognizes VA-ECMO as a viable therapy for refractory septic shock in neonates and children, there is clinical equipoise as to the role of tMCS in adult patients with refractory distributive shock caused by sepsis.[45] Small, single-center studies, which should be interpreted with caution, report highly variable survival ranging from 15% to 70% when VA-ECMO was used for refractory septic shock.[46–49] These studies found that younger adults with acute, profound LV dysfunction had the best outcomes, whereas patients with sepsis, distributive shock, and less severe or normal myocardial function demonstrated worse outcomes.[45–47] In a single-center Korean study of 246 patients with mixed shock and CS treated with VA-ECMO, the authors report higher 30-day (50% versus 43%) and 1-year (68% versus 53%) mortality among patients with mixed shock.[50]

Percutaneous LV assist devices augment CO and dissociate LV and aortic pressures, such that arterial pressure increases whereas peak LV pressure decreases. Based on these desirable hemodynamic effects and 13% improvement in mortality in a recent trial of patients with CS, there is physiologic plausibility for the use of percutaneous LV assist devices in mixed CS, although data are limited to case reports and registries. However, there is likely less potential for benefit in patients with predominant distributive shock with above normal cardiac index and the closer LV end-diastolic pressure is to normal.

We suggest that tMCS device deployment in patients with mixed CS states can be considered when they are part of Cardiogenic Shock Team discussions after complete hemodynamic evaluation, identification of the likely secondary cause(s) of shock, or treatment of potential reversible causes has been unsuccessful. Deployment should be reserved for patients in whom there is meaningful potential to improve insufficient CO and restore end-organ perfusion that outweighs the potential of exacerbating vasoplegia complicating any ongoing bacteremia and device-related complications. Patient and device selection in patients with mixed CS requires further research, but current decisions should be guided by shock etiologies, phenotypes, hemodynamic profile (including SVR), risk of complications, the need for adjunctive vasodilatory medications to achieve safe device use, or requirement for fluid administration to maintain perfusion.

CONCLUSIONS

Mixed CS is a multifactorial and high-acuity syndrome associated with a higher in-hospital mortality compared with pure CS. The potential hemodynamic complexities of this syndrome often necessitate invasive hemodynamic monitoring together with an individualized approach to medical therapy and thoughtful consideration of the risks and benefits of potential tMCS deployment. Herein, we have proposed a classification system for mixed CS that could be used to better identify and phenotype patients in registries and clinical trials.

ARTICLE INFORMATION

Received March 3, 2024; accepted July 10, 2024.

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Acknowledgments

We would like to gratefully acknowledge L. Soulards's help with copyediting the article and graphical revisions.

Sources of Funding

None.

Disclosures

Dr Morrow is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott Laboratories, Abiomed, Amgen, Anthos Therapeutics, Arca Biopharma, AstraZeneca, Daiichi-Sankyo, Intarcia, Janssen, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Regeneron, Roche, Siemens, and Zora Biosciences. Dr Morrow has received consulting fees from Abbott Laboratories, Arca Biopharma, InCarda, Inflammatix, Merck, Novartis, and Roche Diagnostics. Dr Gage has received an educational honorarium from Zoll and is a former member of the Abiomed speaker's bureau. Dr Pöss has received research funding (institutional) from the German Cardiac Society, Dr Rolf M. Schwiete Foundation, German Heart Research Foundation, and Maquet Cardiopulmonary GmbH. The other authors report no conflicts.

Supplemental Material

Figure S1

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